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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,000	SOOD ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *57-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-56* is/are rejected.

7)☒ Claim(s) *50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed January 10, 2007. Currently claims 1-62 are pending. Claims 57-62 are withdrawn.

Any rejections not reiterated below are hereby withdrawn.

The Double Patenting rejections have been overcome by the submission of terminal disclaimers to patents 7, 052,839, 7,033,762, 7,041,812, 7,125,671 and patent applications 11/255,683 and 10/651,582.

This action contains new grounds of rejection.

New Matter Rejections

Claim Rejections - 35 USC § 112

2. Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In claims 1-31, the recitation "with a phosphatase activatable label" appears to be new matter. The specification does not provide basis for the concept of a phosphatase activatable label. Page 20 of remarks file January10, 2007 point to page 19, lines 12-13 for basis for the amendment to a phosphatase activitable label. However, the

specification teaches, "the label is activated after phosphatase treatment, the label attached at the terminal-phosphate position in the terminal-phosphate-labeled nucleotide may be selected from the group." The specification teaches the label is activated after phosphate treatment, but does not teach the label is activated as a result of treatment with a phosphatase. Thus the concept of a "phosphatase activatable label" was not originally disclosed and is new matter.

In claims 1-31, the recitation "wherein said detectable species is readily distinguishable from the labeled polyphosphate or terminal-phosphate labeled nucleoside polyphosphate" appear to be new matter. The specification does not provide basis for the concept of the species is readily detectable from the labeled polyphosphate or terminal phosphate labeled polyphosphate. Page 20 of remarks file January10, 2007 point to pages 4, lines 6-9, page 12, lines 20-23, and page 19, lines 12-22 for basis for the amendment to a readily distinguishable from the labeled polyphosphate or terminal-phosphate labeled nucleoside polyphosphate. However, page 4 teaches the polyphosphate transferring enzyme releases a free label that is distinguishable from the phosphate bound dye. While page 12, lines 20-23, teach a polyphosphate released may be reacted with a phosphatase to produce a detectable signal, but does not teach or suggest the concept the detectable species is readily distinguishable from the labeled polyphosphate or terminal-phosphate labeled nucleotide polyphosphate. Page 19, lines 20-23 teach the label is activated after phosphatase treatment. The specification does not teach that the label is readily distinguishable from the nucleoside polyphosphate or the polyphosphate label.

Claim Objections

3. Claim 50 is objected to because of the following informalities: Claim 50 recites "bodipydyeand derivatives". This is believed to be a typographical error and should be corrected. Appropriate correction is required.

Maintained rejections

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-7, 9, 11-18, 20-23, 27-38, 40, 42-45, 47, 49-50, 55, 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al (WO/2001/94609).

With regards to claim 1, Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released

as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a γ-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is a continuing polymerization assay by adding different nucleoside polyphosphates.

With regards to claim 2, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21). Target nucleic acid is a template.

With regards to claim 3, Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19). Williams teaches oligonucleotides are primers (see page 29, lines 7-18).

With regards to claim 4, Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2).

With regards to claim 5, Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6).

With regards to claim 6, Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29).

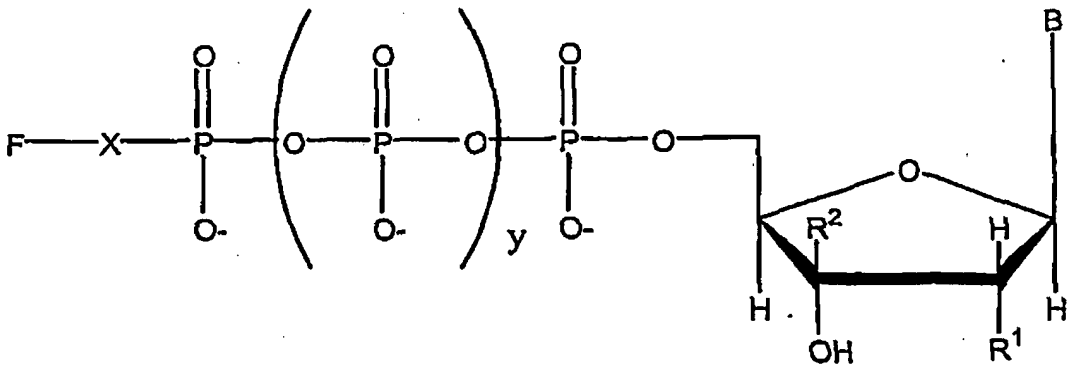
With regards to claim 7, Williams teaches, "the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated" (see page 25, lines 15-16). The amount of pyrophosphate released is thus proportional to the amount of template nucleic acid present. The amount of nucleic acid present is thus quantitated.

With regards to claim 9, Williams teaches a nucleic acid polymerase (see page 4 lines 20-21).

With regards to claims 11 and 12, Williams teaches DNA as a template (see abstract). Instant specification teaches, "'oligonucleotide' includes linear oligomers of nucleotides or derivatives thereof, including deoxyribonucleosides." Oligonucleotide thus encompasses DNA.

With regards to claim 13, Williams teaches sequencing in real time (see abstract). Real time sequencing requires the conducting step and subjecting step to be done simultaneously.

With regards to claim 14, Williams et al teaches the figure at the top of page 15



Williams further teaches in line 21 of page 20, Y can be 0, 1, or 3. Williams thus teaches a polyphosphate with 5 phosphates (2 in the figure plus the 3 of the y depiction). Williams thus teaches 4 or more phosphate groups in the polyphosphate chain.

With regards to claim 15, Williams teaches, "the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated" (see page 25, lines 15-16). As Williams teaches the pyrophosphate has the detectable label, this is a detectable species directly proportional to mount of nucleic acid sequence.

With regards to claim 16, Williams teaches the use other phosphate transferring enzymes that include ATP sulphurylase-luciferase system and phosphatase.

With regards to claim 17, Williams teaches the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6).

With regards to claim 18, Williams teaches the nucleotide sequence of the target DNA can be thereafter be directly read from the order of releases dyes attached to pyrophosphate (see page 24, lines 7-8).

With regards to claim 20, Williams teaches use of fluorescent dyes and chromogenic dyes (see page 16, line 4 and page 24, lines 5-6).

With regards to claim 21 Williams teaches the molecule of the figure on top of page 15. Williams teaches the B is a nucleobase, a sugar moiety is depicted, three phosphates are depicted (the Y in the figure is in line 21 suggested to be , 0, 1, or 3) and the f is a label that can be independently detected upon activation (cleavage).

With regards to claim 22, Williams teaches the use of fluorescent dyes (see page 16, lines 15-23).

Claim 23 encompasses resorufin phosphate.

With regards to claim 23, Williams teaches the use of resorufin (see page 16, line 16). The incorporation of resorufin into the polyphosphate complex of Williams would result in resorufin phosphate or derivatives thereof.

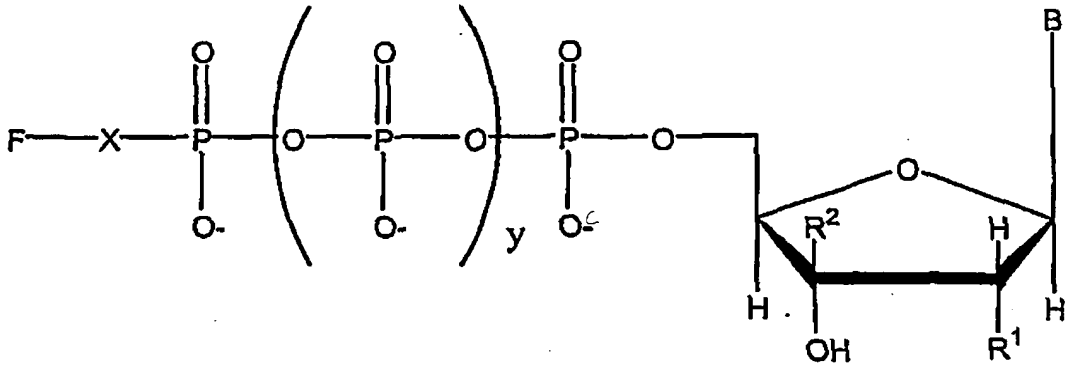
With regards to claims 27 and 28, Williams teaches the use of a nucleoside linked to a pentose at the 1' position, including the 2'-deoxy and 2'-hydroxyl form (see page 8, lines 21-25). Williams et al thus teaches the use of a ribosyl or 2'deoxyribosyl sugar.

With regards to claim 29, Williams et al teaches use of adenine, guanine, cytosine, uracil, thymine, deazaadenine and deazaguanosine. Williams thus teach nitrogen-containing heterocyclic bases.

The addition of terminal phosphate labeled polyphosphates in claims 30 and 31 is interpreted as the incorporation into primer elongation.

With regards to claims 30, 31, 55 and 56, Williams teaches sequencing the target nucleic acid (see page 4, lines 28-29). Sequencing is based on the addition of nucleotides or nucleoside polyphosphates in order to make a complementary strand of the target region. The sequencing method taught by Williams encompasses this, further Williams teachings of the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6) results in sequencing by addition of labeled bases.

With regards to claim 32, Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams et al teaches the figure at the top of page 15



Williams further teaches in line 21 of page 20, Y can be 0, 1, or 3. Williams thus teaches a polyphosphate with 5 phosphates (2 in the figure plus the 3 of the y

depiction). Williams thus teaches 4 or more phosphate groups in the polyphosphate chain.

With regards to claim 33, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21). Target nucleic acid is interpreted as template.

With regards to claim 34, Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19). Williams teaches oligonucleotides are primers (see page 29, lines 7-18).

With regards to claim 35, Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2).

With regards to claim 36, Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6).

With regards to claim 37, Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29).

With regards to claim 38, Williams teaches, "the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated" (see page 25, lines 15-16). The amount of pyrophosphate released is thus proportional to the amount of template nucleic acid present. The amount of nucleic acid present is thus quantitated.

With regards to claim 40, Williams teaches a nucleic acid polymerase (see page 4 lines 20-21).

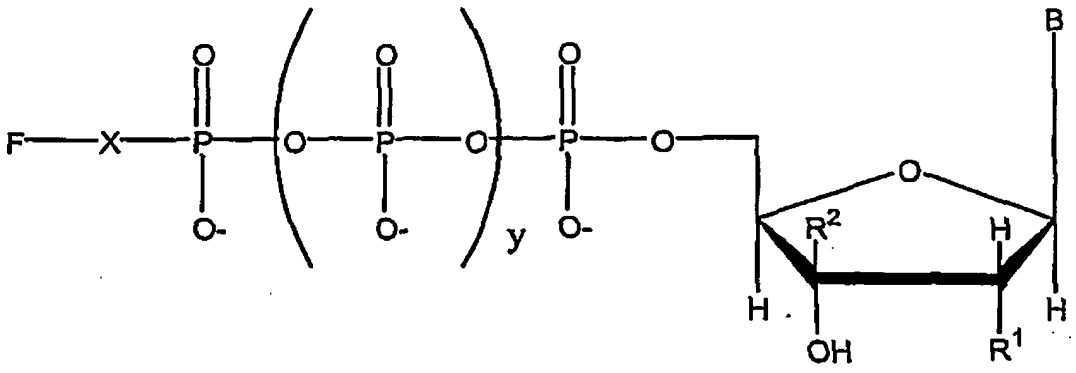
With regards to claims 42 and 43, Williams teaches DNA as a template (see abstract). Instant specification teaches, "'oligonucleotide' includes linear oligomers of nucleotides or derivatives thereof, including deoxyribonucleosides." Oligonucleotide thus encompasses DNA.

With regards to claim 44, Williams teaches, "the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated" (see page 25, lines 15-16). As Williams teaches the pyrophosphate has the detectable label, this is interpreted as detectable species directly proportional to mount of nucleic acid sequence.

With regards to claim 45, Williams teaches the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6).

With, regards to claim 47, Williams teaches use of fluorescent dyes (see page 24, lines 5-6).

With regards to claim 48, Williams et al teaches the figure at the top of page 15



Williams further teaches in line 21 of page 20, Y can be 0, 1, or 3. Williams thus teaches a polyphosphate with 5 phosphates (2 in the figure plus the 3 of the y depiction). Williams thus teaches 4 or more phosphate groups in the polyphosphate chain.

With, regards to claim 49, Williams teaches use of fluorescent dyes and chromogenic dyes (see page 16, line 4 and page 24, lines 5-6).

With regards to claim 50, Williams et al teaches xanthenes, cyanine, coumarin and BODIPY dyes (see page 16, lines 15-22). Williams thus teaches the fluorescent dyes recited.

With regards to claim 50 and 51, Williams teaches the molecule of the figure on top of page 15. Williams teaches the B is a nucleobase, a sugar moiety is depicted, three phosphates are depicted (the Y in the figure is in line 21 suggested to be , 0, 1, or 3) and the f is a label that can be independently detected upon activation (cleavage).

With regards to claims 52 and 53, Williams teaches the use of a nucleoside linked to a pentose at the 1' position, including the 2'-deoxy and 2'-hydroxyl form (see

page 8, lines 21-25). Williams et al thus teaches the use of a ribosyl or 2'deoxyribosyl sugar.

With regards to claim 54, Williams et al teaches use of adenine, guanine, cytosine, uracil, thymine, deazaadenine and deazaguanosine. Williams thus teach nitrogen-containing heterocyclic bases.

Response to arguments

It is noted that the above rejections incorporate new rejections for claims 14, 21-23, 27-29 and 48-54.

The response filed 1/10/2007, asserts on page 20, that the newly amended claims require a phosphatase activatable label that is readily distinguishable from the labeled polyphosphate or nucleotide polyphosphate. The response further asserts that the detectable species generated by Williams method is not readily distinguishable from the labeled polyphosphate. The response further asserts on page 21 that the labeled nucleotide is inert to phosphatase treatment and thus the phosphatase treatment can be carried out simultaneously to the polymerase reaction. The response further asserts, on page 21, that Williams does not teach 4 or more phosphates.

Applicant's arguments have been fully considered but are not found persuasive.

In response to the assertion that Williams et al does not teach readily distinguishable phosphatase activated label or the labeled polyphosphate or labeled nucleotide. The response points out that "the only change phosphatase treatment brings to the label in Williams is a change in charge. This change in charge argued by

the response makes it readily distinguishable from the labeled polyphosphate and labeled polyphosphate nucleotide. Thus Williams teaches the changes in charge associated with the phosphatase cleavage do result in the cleaved label being distinguishable from the labeled nucleotide or labeled nucleotide polyphosphate and anticipates the claimed invention.

The response further asserts that Williams requires separation by charge of the dye labeled pyrophosphate product. However the method has comprising language that allows additional steps in the method. The MPEP states in 211.02

> The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., > Mars Inc. v. H.J. Heinz Co., 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term comprising,' the terms containing' and mixture' are open-ended.").< Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). >In Gillette Co. v. Energizer Holdings Inc., 405 F.3d 1367, 1371-73, 74 USPQ2d 1586, 1589-91 (Fed. Cir. 2005), the court held that a claim to "a safety razor blade unit comprising a guard, a cap, and a group of first, second, and third blades" encompasses razors with more than three blades because the transitional phrase "comprising" in the preamble and the phrase "group of" are presumptively open- ended. "The word comprising' transitioning from the preamble to the body signals that the entire claim is presumptively open-ended." Id. In contrast, the court noted the phrase "group consisting of" is a closed term, which is often used in claim drafting to signal a "Markush group" that is by its nature closed. Id. The court also emphasized that reference to "first," "second," and "third" blades in the claim was not used to show a serial or numerical limitation but instead was used to distinguish or identify the various members of the group. Id.

Thus the teachings of Williams do meet the limitations of the claims.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the labeled nucleotide is inert to phosphatase) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's arguments about claim 32, Williams teaches the use of 5 polyphosphates as in the new rejection above.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 8 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Wittwer et al (US Patent 6174670).

Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule

configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams does not teach quantifying nucleic acid by comparing spectra with a known standard.

However, Wittwer teaches determining the concentration of a nucleic acid by comparison to the fluorescence of a known concentration template (see column 11, line 65 to column 12 line 40). Wittwer teaches this simple method allows quantification of low copy number DNA (see column 39, lines 59-60).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to quantitate the nucleic acid sequences of Williams with Wittwers method of quantitation, because Wittwer teaches it is a simple method for

quantification of low copy number DNA. The ordinary artisan would be motivated to improve Williams method of sequencing because Wittwer teaches a simple method for quantification of low copy number DNA.

Response to Arguments

The response traverses the rejection. The response asserts for the reasons presented for Williams the rejection is improper.

This argument has been considered but is not convincing because Williams does teach the limitations of claims 1 and 32, as previous discussed. Thus the combination of Williams and Wittwer would make the instantly claimed invention obvious.

Thus for the reasons above and those already of record, the rejection is maintained.

8. Claim 10 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Keller et al (US Patent 5656462).

Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid

wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams does not teach the use of an RNA template.

However, Keller et al teaches the use of an RNA template (see column 13, lines 54-55) because it is useful in the preservation and analysis of genes.

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to improve Williams method of sequencing by the use of RNA templates as taught by Keller, because Keller teaches use of RNA allows gene analysis. The ordinary artisan would be motivated to use the RNA template, because Keller teaches the RNA template is useful in preservation and analysis of genes.

Response to Arguments

The response traverses the rejection. The response asserts for the reasons presented for Williams the rejection is improper.

This argument has been considered but is not convincing because Williams does teach the limitations of claims 1 and 32, as discussed above. Thus the combination of Williams and Keller would make the instantly claimed invention obvious.

Thus for the reasons above and those already of record, the rejection is maintained.

9. Claim 19 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Lichenwalter et al (US Patent 5683875).

Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams teaches the use of four deoxynucleotide triphosphates, each labeled with a different color

fluorescent dye (see page 24, lines 5-6). Williams does not teach the use of an antibody as a detection reagent.

However, Lichtenwalter et al teach the use of an antibody to detect elongated nucleic acid complexes (see column 3, lines 27-30, column 3, lines 14-17), because it is a convenient and reliable diagnostic method (column 13, lines 20-21).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to use the antibodies taught by Lichtenwalter to detect the elongation products of Williams, because Lichtenwalter teaches it is a convenient and reliable diagnostic method. The ordinary artisan would be motivated to detect Williams elongation products with Lichtenwalter's antibodies because Lichtenwalter teaches it is a convenient and reliable diagnostic method.

Response to Arguments

The response traverses the rejection. The response asserts for the reasons presented for Williams the rejection is improper.

This argument has been considered but is not convincing because Williams does teach the limitations of claims 1 and 32, as discussed above. Thus the combination of Williams and Lichtenwalter would make the instantly claimed invention obvious.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection

10. Claim 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Hattori et al (US Patent 5,821,095, Published October 13, 1998).

Claim 23 is being rejected as directed to 4-methylumbelliferyl phosphate.

Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams teaches the molecule of the figure on top of page 15. Williams teaches the B is a nucleobase, a

sugar moiety is depicted, three phosphates are depicted (the Y in the figure is in line 21 suggested to be , 0, 1, or 3) and the f is a label that can be independently detected upon activation (cleavage).

Williams does not teach the use of chromogenic dyes 5-bromo-4-chloro-3-indolyl phosphate, 3-indoxyl phosphate, p-nitrophenyl phosphate and derivatives thereof (claim 24), 4-methylumbelliferyl phosphate (claim 23) or 1,2 doixetane (claim 25).

However, Hattori et al teaches the use of p-nitrophenyl phosphate, 5-bromo-4-chloro-3-indolyl phosphate, 4-methylumbelliferone phosphate and chemiluminescent dioxetanes in phosphatase assays (see column 1, lines 53-57). Hattori et al further teaches these substrates allow for a significant improvement in sensitivity of the phosphatase assay.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the substrates of Hattori et al in the method of Williams. One of ordinary skill in the art would be motivated to use Hattori et al substrates, because Hattori et al teaches they result in more sensitive detection.

11. Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Bronstein et al (US Patent 5,112,960 Issue May 12, 1992).

Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target

nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams teaches the molecule of the figure on top of page 15. Williams teaches the B is a nucleobase, a sugar moiety is depicted, three phosphates are depicted (the Y in the figure is in line 21 suggested to be , 0, 1, or 3) and the f is a label that can be independently detected upon activation (cleavage).

Williams et al does not teach the use of chemiluminescent compounds 1,2-dioxetane or the compounds 2-chloro-5-(4-methoxyspiro[1,2-dioxetane-3,2'-(5-chloro-)tricyclo [3,3,1 - 13,7]_decan]_ 1 -yl)- 1 -phenyl phosphate, chloroadamant-2' -ylidenemethoxyphenoxy phosphorylated dioxetane, 3-(2'-spiroadamantane)-4-methoxy-4-(3"-phosphoryloxy)phenyl-1,2-dioxetane and derivatives thereof .

In addition, the court have stated:

> similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972) (see MPEP 2144.08(d)).

The teachings of Bronstein et al in the structure of the abstract is a derivative of the recited compounds. Bronstein teaches the compounds of her invention allow for the studying of chemical or biological substances (including nucleic acids) to allow structures to be determined and quantified (see column 2, lines 5-9). Bronstein et al teaches her enzymatically cleavable 1,2 dioxetanes allow for quick detection and steady state light emission (see column 3, lines 7-10). Bronstein et al teaches that these compounds are cleavable by alkaline phosphatases and decrease the time necessary to conduct assays (see column 3, lines 25-28, column 4, lines 62-65). Bronstein et al further teaches these compounds provide for improved signal (see column 5, lines 3-8).

Therefore it would have been prima facie obvious to one of ordinary skill of the art at the time the invention was made to improve the method of pyrophosphatase sequencing taught by Williams by use of the 1,2-dioxetane taught by Bronstein. One of ordinary skill in the art would be motivated to use the 1,2 dioxetane compounds of Bronstein because Bronstein teaches it allows rapid detection and quantification. The ordinary artisan would also be motivated to combine the 1,2 dioxetanes of Bronstein and the method of Williams, because Bronstein teaches the 1,2 dioxetanes are cleavable by alkaline phosphatase (which are commonly used in pyrophosphate

sequencing) and decrease the assay time. The combined teachings of Williams and Bronstein would result in a fast quantitative method of detecting the alkaline phosphatase activity of pyrophosphate sequencing.

Summary

No claims are allowed over prior art cited.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

J. Goldberg

JEANINE A. GOLDBERG
PRIMARY EXAMINER
3/28/07

Steven Pohnert